



Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV.

Downloaded from <https://aidsinfo.nih.gov/guidelines> on 8/31/2020

Visit the AIDSinfo website to access the most up-to-date guideline.

Register for e-mail notification of guideline updates at <https://aidsinfo.nih.gov/e-news>.

Cryptococcosis (Last updated August 17, 2016; last reviewed June 26, 2019)

NOTE: Update in Progress

Epidemiology

Most HIV-associated cryptococcal infections are caused by *Cryptococcus neoformans*, but occasionally *Cryptococcus gattii* is the etiology. *C. neoformans* is found worldwide, whereas *C. gattii* most often is found in Australia and similar subtropical regions and in the Pacific Northwest. Before the era of effective antiretroviral therapy (ART), approximately 5% to 8% of HIV-infected patients in developed countries were diagnosed with disseminated cryptococcosis.¹ Current estimates indicate that every year, nearly 1 million cases of cryptococcal meningitis are diagnosed worldwide and the disease accounts for more than 600,000 deaths.² With the availability of effective ART, the incidence of the disease has declined substantially in areas with ART access, and most new infections are being recognized in patients recently diagnosed with HIV infection.³ Most cases are observed in patients who have CD4 T lymphocyte (CD4) cell counts <100 cells/ μ L.

Clinical Manifestations

In HIV-infected patients, cryptococcosis commonly presents as a subacute meningitis or meningoencephalitis with fever, malaise, and headache.¹ Classic meningeal symptoms and signs, such as neck stiffness and photophobia, occur in only one-quarter to one-third of patients. Some patients experience encephalopathic symptoms, such as lethargy, altered mentation, personality changes, and memory loss that are usually a result of increased intracranial pressure.

Cryptococcosis usually is disseminated when diagnosed in an HIV-infected patient. Any organ of the body can be involved, and skin lesions may show myriad different manifestations, including umbilicated skin lesions mimicking molluscum contagiosum. Isolated pulmonary infection is also possible; symptoms and signs include cough and dyspnea in association with an abnormal chest radiograph, which typically demonstrates lobar consolidation, although nodular infiltrates have been reported. Pulmonary cryptococcosis may present as acute respiratory distress syndrome and mimic *Pneumocystis pneumonia*.

Diagnosis

Analysis of cerebrospinal fluid (CSF) generally demonstrates mildly elevated levels of serum protein, low-to-normal glucose concentrations, and pleocytosis consisting mostly of lymphocytes. Some HIV-infected patients will have very few CSF inflammatory cells, but a Gram's stain preparation, or an India ink preparation if available, may demonstrate numerous yeast forms. The opening pressure in the CSF may be elevated, with pressures ≥ 25 cm H₂O occurring in 60% to 80% of patients.^{4,5}

Cryptococcal disease can be diagnosed through culture, CSF microscopy, or by cryptococcal antigen (CrAg) detection. In patients with HIV-related cryptococcal meningitis, 55% of blood cultures and 95% of CSF cultures are positive and visible colonies can be detected within 7 days. *Cryptococcus* may be occasionally identified on a routine Gram stain preparation of CSF. India ink staining of CSF demonstrates encapsulated yeast in 60% to 80% of cases, but many laboratories in the United States no longer perform this test. CSF CrAg is usually positive in patients with cryptococcal meningoencephalitis. Serum CrAg is usually positive in both meningeal and non-meningeal infections and may be present weeks to months before symptom onset.⁶ A positive serum CrAg should prompt a lumbar puncture to rule out meningeal disease. Three methods exist for antigen detection: latex agglutination, enzyme immunoassays, and lateral flow assay (a newly developed dipstick test). Testing for the antigen in the serum is a useful initial screening tool in diagnosing cryptococcosis in HIV-infected patients,⁷ and it may be particularly useful when a lumbar puncture is delayed or refused.

Preventing Exposure

Cryptococcus is ubiquitous in the environment. HIV-infected patients cannot completely avoid exposure to

C. neoformans or *C. gattii*. Limited epidemiological evidence suggests that exposure to aged bird droppings may increase risk of infection.

Preventing Disease

The incidence of cryptococcal disease is low among HIV-infected patients in the United States. However, a recent report from the United States indicates that among HIV-infected patients with peripheral blood CD4 counts ≤ 100 cells/ μL , the prevalence of cryptococcal antigenemia, a harbinger of disease, was 2.9%, and prevalence was 4.3% for those with CD4 counts ≤ 50 cells/ μL .⁸ Routine testing for serum CrAg in newly diagnosed HIV-infected persons with no overt clinical signs of meningitis is recommended by some experts for patients whose CD4 counts are ≤ 100 cells/ μL and particularly in those with CD4 counts ≤ 50 cells/ μL . A positive test should prompt CSF evaluation for meningitis.

Prospective, controlled trials indicate that prophylactic fluconazole or itraconazole can reduce the frequency of primary cryptococcal disease in patients who have CD4 counts < 100 cells/ μL .^{9,10} However, in the United States, primary prophylaxis in the absence of a positive serum cryptococcal antigen test is not recommended because of the relative infrequency of cryptococcal disease, lack of survival benefit associated with prophylaxis, possibility of drug interactions, potential antifungal drug resistance, and cost (**BII**). Patients with isolated cryptococcal antigenemia without meningitis can be treated similarly to patients with focal pulmonary cryptococcosis (see below).

Treating Disease

Treating cryptococcosis consists of three phases: induction, consolidation, and maintenance therapy. For induction treatment for cryptococcal meningitis and other forms of extrapulmonary cryptococcosis, an amphotericin B formulation given intravenously, in combination with oral flucytosine, is recommended (**AI**). Historically, amphotericin B deoxycholate has been the preferred formulation at a dose of 0.7 to 1.0 mg/kg daily. However, there is a growing body of evidence that lipid formulations of amphotericin B are effective for disseminated cryptococcosis, particularly in patients who experience clinically significant renal dysfunction during therapy or who are likely to develop it. The non-comparative CLEAR study demonstrated a 58% response rate in HIV-infected patients treated with amphotericin B lipid complex at mean dose of 4.4 mg/kg daily.¹¹ In a Dutch and Australian study, a 3-week course of liposomal amphotericin B (4 mg/kg daily) resulted in more rapid sterilization of CSF than amphotericin B deoxycholate (0.7 mg/kg daily).¹² A recently published comparison of amphotericin B deoxycholate (0.7 mg/kg daily), and liposomal amphotericin B (AmBisome®) (3 mg/kg or 6 mg/kg daily) showed similar efficacy for the three regimens, but nephrotoxicity was lower with 3 mg/kg daily liposomal amphotericin B.¹³

Amphotericin B formulations should be combined with flucytosine at a dose of 100 mg/kg daily in 4 divided doses for ≥ 2 weeks in patients with normal renal function, and this is the preferred regimen for primary induction therapy (**AI**). Based on available clinical trial data, a daily dose of 3 to 4 mg/kg of liposomal amphotericin B is the recommended amphotericin B formulation (**AI**). Amphotericin B deoxycholate at a dose of 0.7 mg/kg daily is equally efficacious (**AI**) and can be used if cost is an issue and the risk of renal dysfunction is low. Amphotericin B lipid complex at a dose of 5 mg/kg daily can be used as an alternative amphotericin B preparation, although fewer data are available to support its use (**BII**).

When using flucytosine, serum levels of flucytosine, if this assay is available, should be obtained 2 hours post-dose after 3 to 5 doses have been administered. Serum levels should be between 25 and 100 mg/L.¹⁶ Renal function should be monitored closely and the flucytosine dose adjusted accordingly for patients with renal impairment. The dose of flucytosine should be reduced by 50% for every 50% decline in creatinine clearance. The addition of flucytosine to amphotericin B during acute treatment is associated with more rapid sterilization of CSF.¹⁴⁻¹⁷ A recent randomized clinical trial also showed that the combination of amphotericin B deoxycholate at a dose of 1.0 mg/kg daily combined with flucytosine was associated with improved survival compared to the same dose of amphotericin B without flucytosine.¹⁸

Amphotericin B deoxycholate in combination with 400 mg of fluconazole daily was inferior to amphotericin B in combination with flucytosine for clearing *Cryptococcus* from CSF.¹⁹ However, in 2 randomized trials, amphotericin B plus 800 mg of fluconazole daily compared favorably with amphotericin B alone.^{19,20} Therefore, amphotericin B deoxycholate alone or combined with fluconazole at 800 mg daily (**BI**) or lipid-formulation amphotericin B alone or combined with fluconazole at 800 mg daily (**BIII**) may be viable options in some circumstances but are less preferable alternatives than lipid-formulation amphotericin B combined with flucytosine (**BI**).

Fluconazole (400 mg daily) combined with flucytosine is also a potential alternative to amphotericin B regimens (**BII**).²¹ Some experts would use 800 mg daily (**BIII**). Fluconazole alone, based on early fungicidal activity, is inferior to amphotericin B²² for induction therapy and is recommended only for patients who cannot tolerate or do not respond to standard treatment. If it is used for primary induction therapy, the starting daily dose should be 1200 mg (**CI**).²³

After at least 2 weeks of successful induction therapy—defined as substantial clinical improvement and a negative CSF culture after repeat lumbar puncture—amphotericin B and flucytosine can be discontinued and follow-up or consolidation therapy initiated with fluconazole at 400 mg daily (**AI**). This therapy should continue for at least 8 weeks (**AI**).^{14,15,24} Subsequently, the fluconazole should be reduced to 200 mg daily and continued as chronic maintenance therapy to complete at least 1 year of azole therapy (see the Preventing Recurrence section below).²⁵ Itraconazole, at the same dosage as fluconazole, can be used as an alternative (**CI**), but it is clearly inferior to fluconazole.²⁴ Limited data are available for the newer triazoles, voriconazole and posaconazole, as either primary or maintenance therapy for patients with cryptococcosis. Most of the data on use of these extended-spectrum triazole antifungals have been reported for treatment of refractory cases, with success rates of approximately 50%.^{26,27} At this time, the role of posaconazole and voriconazole in the management of cryptococcosis is not established. Voriconazole should be used cautiously with HIV protease inhibitors and efavirenz.

Non-central-nervous-system (CNS), extrapulmonary cryptococcosis, and diffuse pulmonary disease should be treated similarly to CNS disease (**BIII**). For mild-to-moderate symptoms and focal pulmonary infiltrates, treatment with fluconazole (400 mg daily for 12 months) combined with effective ART is appropriate (**BIII**). Treatment is the same for patients with an isolated positive serum cryptococcal antigen test (**BIII**). **All patients should have their CSF sampled to rule out CNS disease.**

Special Considerations with Regard to Starting ART

Optimal timing for ART initiation in patients with acute cryptococcal meningitis is controversial. One randomized, controlled trial that included 35 patients with cryptococcal meningitis suggested that ART was safe when started within the first 14 days of diagnosis.²⁸ A subsequent study from Africa demonstrated significantly worse outcomes in 54 patients started on ART within 72 hours of cryptococcal meningitis diagnosis compared with those in which ART was delayed for at least 10 weeks.²⁹ However, in the latter study, cryptococcal meningitis was managed with fluconazole alone, and ART consisted of nevirapine, stavudine, and lamivudine. Neither fluconazole alone nor the latter ART regimen are recommended as preferred initial treatment in the United States. A randomized clinical trial conducted at 2 sites in Africa among hospitalized patients with acute cryptococcal meningitis³⁰ compared patients with cryptococcal meningitis who were started on ART within 1 to 2 weeks (median 8 days) after fungal diagnosis with patients in whom ART was deferred until 5 weeks (median 36 days) after diagnosis. In contrast to the other African study, this study used deoxycholate amphotericin B (0.7–1.0 mg/kg daily) plus 800 mg of fluconazole daily during the induction phase of antifungal treatment. There was a significant increase in 6-month mortality in the early ART group compared with the deferred ART group (45% vs 30%, $P = 0.03$). This increase was most pronounced during the first 8 to 30 days of study ($P = 0.007$). The difference in mortality was even greater between the early ART group and the deferred ART group if the CSF white cell count was <5 cells/ μL ($P = 0.008$). While the excess of deaths in the early ART group was attributed to cryptococcosis, it is unclear if they were directly due to meningitis and its sequelae or due to immune reconstitution inflammatory syndrome (IRIS).

Based on the studies cited above and on expert opinion, it is prudent to delay initiation of ART at least until after completion of antifungal induction therapy (the first 2 weeks) and possibly until the total induction/consolidation phase (10 weeks) has been completed. Delay in ART may be particularly important in those with evidence of increased intracranial pressure or in those with low CSF white blood cell counts. Hence, the timing of ART administration should be considered between 2 and 10 weeks after the start of antifungal therapy with the precise starting dates based on individual conditions and local experience (**BIII**). If effective ART is to begin prior to 10 weeks, the treating physicians should be prepared to aggressively address complications caused by IRIS, such as elevated intracranial pressure (ICP).

For other forms of cryptococcosis, where the risk of IRIS appears to be much lower, the optimal time to begin ART and antifungal therapy is not clear. However, it would seem prudent to delay initiation of ART by 2 to 4 weeks after starting antifungal therapy (**BIII**).

All the triazole antifungals have the potential for complex, and possibly bidirectional, interactions with certain antiretroviral agents. [Table 5](#) lists these interactions and recommendations for dosage adjustments, where feasible.

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

ICP elevations can cause clinical deterioration despite a microbiologic response, and they are more likely to occur if the CSF opening lumbar pressure is $\geq 25\text{cm H}_2\text{O}$ ^{4,14} when obtained in the lateral decubitus position with good manometrics assured. In 1 large clinical trial, increased ICP was associated with 93% of deaths during the first 2 weeks of therapy and 40% of deaths during weeks 3 to 10.⁴ Although it is uncertain which patients with high opening lumbar pressures will deteriorate, those with symptoms and signs of ICP require immediate clinical intervention.

Lumbar opening pressure should be measured in all patients with cryptococcal meningitis at the time of diagnosis. Measures to decrease ICP should be used for all patients with confusion, blurred vision, papilledema, lower extremity clonus, or other neurologic signs of increased pressure. Drainage of CSF via lumbar puncture is recommended for initial management. One approach is to remove a volume of CSF (typically 20–30 mL) that at least halves the opening pressure³¹ and repeat daily until symptoms and signs consistently improve. CSF shunting through a lumbar drain or ventriculostomy should be considered for patients who cannot tolerate repeated lumbar punctures or in whom signs and symptoms of cerebral edema persist after multiple lumbar taps (**BIII**). Corticosteroids and mannitol have been shown to be ineffective in managing ICP and **are not recommended** (**AIII**). Acetazolamide **should not be used** as therapy for increased ICP management since it may cause hyperchloremic acidosis and does not result in a decrease in ICP (**AI**).³² A randomized study compared a 6-week course of a tapering dose of dexamethasone among 451 Asian and African patients with HIV infection and cryptococcal meningitis who received amphotericin B deoxycholate plus fluconazole as the induction antifungal regimen. Compared to those receiving placebo, there was no improvement in survival at 10 weeks and dexamethasone was associated with more adverse events.³³ These data support the recommendation that corticosteroids should not routinely be used during induction therapy for HIV-associated cryptococcal meningitis unless they are being used for IRIS (**AI**).

After the first 2 weeks of treatment, many experts would advocate a repeat lumbar puncture to ensure that viable organisms have been cleared from the CSF. Even in patients who have clinical improvement, positive CSF cultures after 2 weeks of therapy are predictive of future relapse and less favorable outcomes. In such cases, some experts would continue amphotericin B plus flucytosine until the CSF cultures are negative (**BIII**). Monitoring titers of cryptococcal polysaccharide antigen in serum or CSF is of no value in determining response to therapy and **is not recommended**. If new symptoms or clinical findings occur later, a repeat lumbar puncture, with measurement of opening lumbar pressure and CSF culture, should be performed.

Patients treated with amphotericin B formulations should be monitored for dose-dependent nephrotoxicity and electrolyte disturbances. Pre-infusion administration of 500 to 1000 mL of normal saline appears to reduce the risk of nephrotoxicity during amphotericin B treatment. Thirty minutes before infusion,

acetaminophen (650 mg) and diphenhydramine (25–50 mg) or hydrocortisone (50–100 mg) typically are administered in an attempt to ameliorate infusion-related adverse reactions (**BIII**), but data supporting these practices are scant. Meperidine (25–50 mg titrated during infusion) is effective for preventing and treating amphotericin B-associated rigors (**BII**).

In patients receiving flucytosine, dosage should be adjusted based on changes in creatinine clearance and can be guided by flucytosine levels. Peak serum flucytosine levels should be obtained 2 hours after an oral dose and the therapeutic range is between 25 and 100 mg/L. Alternatively, frequent (i.e., at least biweekly) blood counts can be performed to detect development of cytopenia. Patients treated with flucytosine also should be monitored for hepatotoxicity and gastrointestinal toxicities.

An estimated 30% of HIV-infected patients with cryptococcal meningitis experience IRIS after initiation or reinstitution of effective ART.^{34,35} Patients who have cryptococcal IRIS are more likely to be antiretroviral naive, have higher HIV RNA levels, and have less CSF inflammation on initial presentation.³⁶ The risk of IRIS may be decreased in those with negative CSF cultures at the time of antiretroviral initiation.³⁷ Distinguishing IRIS from treatment failure may be difficult. In general, cryptococcal IRIS presents with worsening clinical disease despite microbiological evidence of effective antifungal therapy,^{36,38} whereas treatment failure is associated with continued positive cultures. The appropriate management strategy for IRIS is to continue both ART and antifungal therapy and reduce elevated ICP, if present (**AII**). In patients with severe symptoms of IRIS, some specialists recommend a brief course of glucocorticosteroids (**CIII**), but data-based management strategies have not been developed.

The risk of IRIS appears to be much lower with other forms of cryptococcosis; IRIS may present as lymphadenitis, cutaneous abscesses, or bony lesions.³⁹ Management is similar to that for IRIS associated with cryptococcal meningitis, including continuing ART, initiating or continuing antifungal therapy (**AIII**), and considering glucocorticoids (**CIII**).

Managing Treatment Failure

Treatment failure is defined as a lack of clinical improvement and continued positive cultures after 2 weeks of appropriate therapy, including management of increased ICP; or as a relapse after an initial clinical response, defined as recurrence of symptoms with a positive CSF culture after ≥ 4 weeks of treatment. Direct primary fluconazole resistance with *C. neoformans* has been reported in the United States but is uncommon.⁴⁰ Therefore, susceptibility testing is not routinely recommended for initial management of cryptococcosis. Isolates collected to evaluate for persistence or relapse should, however, be checked for susceptibility and compared with the original isolate. While clinical data are lacking, strains with minimum inhibitory concentrations against fluconazole ≥ 16 $\mu\text{g/mL}$ in patients with persistent disease or relapse may be considered resistant.⁴¹

Optimal therapy for patients with treatment failure has not been established. Patients who fail to respond to induction with fluconazole monotherapy should be switched to amphotericin B, with or without flucytosine. Those initially treated with an amphotericin B formulation should remain on it until a clinical response occurs. Liposomal amphotericin B (4–6 mg/kg daily) or amphotericin B lipid complex (5 mg/kg daily) is better tolerated and has greater efficacy than deoxycholate formulation in this setting^{12,13,42} and should be considered when initial treatment with other regimens fails (**AII**).

Higher doses of fluconazole in combination with flucytosine also may be useful (**BIII**). Echinocandins have no activity against *Cryptococcus* spp. and **are not recommended** for clinical management of cryptococcosis (**AII**). The newer triazoles—posaconazole and voriconazole—have activity against *Cryptococcus* spp. *in vitro* and may have a role in salvage therapy, but probably offer no specific advantages over fluconazole unless *in vitro* susceptibility testing indicates fluconazole resistance. Most clinical failures are a result of inadequate induction therapy, drug interactions that interfere with treatment, or the development of IRIS and are not due to drug resistance.

Preventing Recurrence

When to Start Chronic Suppressive Therapy

Patients who have completed the first 10 weeks of induction and consolidation therapy for acute cryptococcosis should be given chronic maintenance or suppressive therapy with 200 mg of fluconazole daily (**AI**). Itraconazole is inferior to fluconazole for preventing relapse of cryptococcal disease (**CI**).²⁴

When to Stop Chronic Suppressive Therapy

Only a small number of patients have been evaluated for relapse after successful antifungal therapy for cryptococcosis and discontinuation of secondary prophylaxis while on ART. In a European study, recurrence of cryptococcosis was not seen among 39 subjects on potent ART whose antifungal therapy was discontinued. In this cohort, when maintenance therapy was stopped, the median CD4 cell count was 297 cells/ μ L, the median HIV RNA concentration was <500 copies/mL, and the median time on potent ART was 25 months.⁴³ A prospective, randomized study of 60 patients in Thailand documented no recurrences of cryptococcosis during 48 weeks of follow-up among 22 patients whose antifungal therapy was discontinued after having achieved a CD4 count >100 cells/ μ L with a sustained undetectable HIV RNA level for 3 months on potent ART.⁴⁴ Given these data and inference from data on discontinuation of secondary prophylaxis for other HIV-associated opportunistic infections, it is reasonable to discontinue chronic antifungal maintenance therapy for cryptococcosis in patients whose CD4 cell counts are \geq 100 cells/ μ L, who have undetectable viral loads on ART for >3 months, and who have received a minimum of 1 year of azole antifungal chronic maintenance therapy after successful treatment of cryptococcosis (**BII**).⁴⁵ Secondary prophylaxis should be reinitiated if the CD4 count decreases again to <100 cells/ μ L (**AIII**).

Special Considerations During Pregnancy

The diagnosis of cryptococcal infections during pregnancy is similar to that in non-pregnant adults. Treatment should be initiated promptly after a diagnosis is confirmed. It should be emphasized that the postpartum period may be a high-risk period for the development of IRIS.

Lipid formulations of amphotericin B are the preferred initial regimen for the treatment of cryptococcal meningoencephalitis, disseminated disease, or severe pulmonary cryptococcosis in pregnant patients. Extensive clinical experience with amphotericin has not documented teratogenicity. Neonates born to women on chronic amphotericin B at delivery should be evaluated for renal dysfunction and hypokalemia.

Flucytosine was teratogenic in animal studies, and human experience is limited to case reports and small series. Therefore, its use should be considered only when the benefits outweigh its risks to the fetus (**CIII**).

Congenital malformations similar to those observed in animals, including craniofacial and limb abnormalities, have been reported in infants born to mothers who received fluconazole at doses of \geq 400 mg/day or more through or beyond the first trimester of pregnancy.⁴⁶ Although several cohort studies have shown no increased risk of birth defects with early pregnancy exposure, most of these studies involved low doses and short-term exposure to fluconazole.^{47,48} Based on the reported birth defects, the FDA has changed the pregnancy category for fluconazole from C to D for any use other than a single, low dose for treatment of vaginal candidiasis (<http://www.fda.gov/Drugs/DrugSafety/ucm266030.htm>). Use of fluconazole in the first trimester should be considered only if the benefits clearly outweigh risks. For pregnant women, amphotericin should be continued throughout the first trimester. After the first trimester, switching to oral fluconazole may be considered, if clinically appropriate.

Although there are case reports of birth defects in infants exposed to itraconazole, prospective cohort studies of over 300 women with first trimester exposure did not show an increased risk of malformation.^{49,50} However, in general azole antifungals **should be avoided** during the first trimester of pregnancy (**BIII**). Voriconazole and posaconazole are teratogenic and embryotoxic in animal studies, voriconazole at doses lower than recommended human doses; there are no adequate controlled studies in humans. These drugs

should be avoided in pregnancy, especially in the first trimester (**AIII**).

Recommendations for Treating Cryptococcosis (page 1 of 2)

Treating Cryptococcal Meningitis

Treatment for cryptococcosis consists of 3 phases: induction, consolidation, and maintenance therapy.

Induction Therapy (For At Least 2 Weeks, Followed by Consolidation Therapy)

Preferred Regimens:

- Liposomal amphotericin B 3–4 mg/kg IV daily plus flucytosine 25 mg/kg PO QID (**AI**); *or*
- Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily plus flucytosine 25 mg/kg PO QID (**AI**)—if cost is an issue and the risk of renal dysfunction is low

Note: Flucytosine dose should be adjusted in renal impairment (see [Table 7](#)).

Alternative Regimens:

- Amphotericin B lipid complex 5 mg/kg IV daily plus flucytosine 25 mg/kg PO QID (**BII**); *or*
- Liposomal amphotericin B 3–4 mg/kg IV daily plus fluconazole 800 mg PO or IV daily (**BIII**); *or*
- Amphotericin B (deoxycholate 0.7–1.0 mg/kg IV daily) plus fluconazole 800 mg PO or IV daily (**BI**); *or*
- Liposomal amphotericin B 3–4 mg/kg IV daily alone (**BI**); *or*
- Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily alone (**BI**); *or*
- Fluconazole 400 mg PO or IV daily plus flucytosine 25 mg/kg PO QID (**BII**); *or*
- Fluconazole 800 mg PO or IV daily plus flucytosine 25 mg/kg PO QID (**BIII**); *or*
- Fluconazole 1200 mg PO or IV daily alone (**CI**)

Consolidation Therapy (For At Least 8 Weeks, Followed by Maintenance Therapy)

- To begin after at least 2 weeks of successful induction therapy (defined as substantial clinical improvement and a negative CSF culture after repeat LP)

Preferred Regimen:

- Fluconazole 400 mg PO or IV once daily (**AI**)

Alternative Regimen:

- Itraconazole 200 mg PO BID (**CI**)

Maintenance Therapy

Preferred Regimen:

- Fluconazole 200 mg PO for at least 1 year (**AI**)—see below for recommendation of when to stop maintenance therapy

Stopping Maintenance Therapy

*If the Following Criteria are Fulfilled (**BII**):*

- Completed initial (induction, consolidation) therapy, and at least 1 year on maintenance therapy, *and*
- Remains asymptomatic from cryptococcal infection, *and*
- CD4 count ≥ 100 cells/ μ L for ≥ 3 months and suppressed HIV RNA in response to effective ART

Restarting Maintenance Therapy:

- If CD4 count declines to ≤ 100 cells/ μ L (**AIII**)

Treating Non-CNS, Extrapulmonary Cryptococcosis and Diffuse Pulmonary Disease:

- Same treatment as for CNS disease (**BIII**)

Treating Non-CNS Cryptococcosis Focal Pulmonary Disease and Isolated Cryptococcal Antigenemia:

- Fluconazole 400 mg PO daily for 12 months (**BIII**)

Recommendations for Preventing and Treating Cryptococcosis (page 2 of 2)

Other Considerations:

- Addition of flucytosine to amphotericin B has been associated with more rapid sterilization of CSF, decreased risk for subsequent relapse, and improved survival.
- When flucytosine is used, serum levels (if available) should be monitored (2 hours post-dose, after 3–5 doses) and drug concentration should be between 25–100 mg/L).
- Opening pressure should always be measured when a LP is performed. Repeated LPs or CSF shunting are essential to effectively manage symptomatic increased ICP.
- In a randomized, controlled trial, a 6-week course of tapering doses of dexamethasone as adjunctive therapy for cryptococcal meningitis did not improve 10-week survival when compared to placebo, and resulted in a higher rate of adverse events. Corticosteroids should not be routinely used during induction therapy unless it is used for management of IRIS **(AI)**.
- Corticosteroids and mannitol are ineffective in reducing ICP and are NOT recommended **(BII)**.
- Infection due to *C. gattii* should be treated similarly to *C. neoformans* **(BIII)**.
- All the triazole antifungals have the potential to interact with certain antiretroviral agents and other anti-infective agents. These interactions are complex and can be bidirectional. [Table 5](#) lists these interactions and recommends dosage adjustments where feasible.

Key to Acronyms: BID = twice daily; CD4 = CD4 T lymphocyte cell; CNS = central nervous system; CSF = cerebrospinal fluid; ICP = intracranial pressure; IV = intravenous; LP = lumbar puncture; PO = orally; QID = four times a day

References

1. Aberg J, WG. P. Cryptococcosis. In: Dolin R MH, Saag MS, ed. *AIDS Therapy*. New York, NY: Churchill Livingstone; 2002:498-510.
2. Park BJ, Wannemuehler KA, Marston BJ, Govender N, Pappas PG, Chiller TM. Estimation of the current global burden of cryptococcal meningitis among persons living with HIV/AIDS. *AIDS*. Feb 20 2009;23(4):525-530. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19182676>.
3. Mirza SA, Phelan M, Rimland D, et al. The changing epidemiology of cryptococcosis: an update from population-based active surveillance in 2 large metropolitan areas, 1992-2000. *Clin Infect Dis*. Mar 15 2003;36(6):789-794. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12627365>.
4. Graybill JR, Sobel J, Saag M, et al. Diagnosis and management of increased intracranial pressure in patients with AIDS and cryptococcal meningitis. The NIAID Mycoses Study Group and AIDS Cooperative Treatment Groups. *Clin Infect Dis*. Jan 2000;30(1):47-54. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10619732>.
5. Bicanic T, Brouwer AE, Meintjes G, et al. Relationship of cerebrospinal fluid pressure, fungal burden and outcome in patients with cryptococcal meningitis undergoing serial lumbar punctures. *AIDS*. Mar 27 2009;23(6):701-706. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19279443>.
6. French N, Gray K, Watera C, et al. Cryptococcal infection in a cohort of HIV-1-infected Ugandan adults. *AIDS*. May 3 2002;16(7):1031-1038. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11953469>.
7. Powderly WG, Cloud GA, Dismukes WE, Saag MS. Measurement of cryptococcal antigen in serum and cerebrospinal fluid: value in the management of AIDS-associated cryptococcal meningitis. *Clin Infect Dis*. May 1994;18(5):789-792. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8075272>.
8. McKenney J, Bauman S, Neary B, et al. Prevalence, correlates, and outcomes of cryptococcal antigen positivity among patients with AIDS, United States, 1986-2012. *Clin Infect Dis*. Mar 15 2015;60(6):959-965. Available at <http://www.ncbi.nlm.nih.gov/pubmed/25422390>.
9. Powderly WG, Finkelstein D, Feinberg J, et al. A randomized trial comparing fluconazole with clotrimazole troches for the prevention of fungal infections in patients with advanced human immunodeficiency virus infection. NIAID AIDS Clinical Trials Group. *N Engl J Med*. Mar 16 1995;332(11):700-705. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7854376>.
10. McKinsey DS, Wheat LJ, Cloud GA, et al. Itraconazole prophylaxis for fungal infections in patients with advanced human immunodeficiency virus infection: randomized, placebo-controlled, double-blind study. National Institute of Allergy and Infectious Diseases Mycoses Study Group. *Clin Infect Dis*. May 1999;28(5):1049-1056. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10544444>.

www.ncbi.nlm.nih.gov/pubmed/10452633.

11. Baddour LM, Perfect JR, Ostrosky-Zeichner L. Successful use of amphotericin B lipid complex in the treatment of cryptococcosis. *Clin Infect Dis*. May 1 2005;40 Suppl 6:S409-413. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15809927>.
12. Leenders AC, Reiss P, Portegies P, et al. Liposomal amphotericin B (AmBisome) compared with amphotericin B both followed by oral fluconazole in the treatment of AIDS-associated cryptococcal meningitis. *AIDS*. Oct 1997;11(12):1463-1471. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9342068>.
13. Hamill RJ, Sobel JD, El-Sadr W, et al. Comparison of 2 doses of liposomal amphotericin B and conventional amphotericin B deoxycholate for treatment of AIDS-associated acute cryptococcal meningitis: a randomized, double-blind clinical trial of efficacy and safety. *Clin Infect Dis*. Jul 15 2010;51(2):225-232. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20536366>.
14. van der Horst CM, Saag MS, Cloud GA, et al. Treatment of cryptococcal meningitis associated with the acquired immunodeficiency syndrome. National Institute of Allergy and Infectious Diseases Mycoses Study Group and AIDS Clinical Trials Group. *N Engl J Med*. Jul 3 1997;337(1):15-21. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9203426>.
15. Saag MS, Graybill RJ, Larsen RA, et al. Practice guidelines for the management of cryptococcal disease. Infectious Diseases Society of America. *Clin Infect Dis*. Apr 2000;30(4):710-718. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10770733>.
16. Dromer F, Mathoulin-Pelissier S, Launay O, Lortholary O, French Cryptococcosis Study G. Determinants of disease presentation and outcome during cryptococcosis: the CryptoA/D study. *PLoS Med*. Feb 2007;4(2):e21. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17284154>.
17. Dromer F, Bernede-Bauduin C, Guillemot D, Lortholary O, French Cryptococcosis Study G. Major role for amphotericin B-flucytosine combination in severe cryptococcosis. *PLoS One*. 2008;3(8):e2870. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18682846>.
18. Day JN, Chau TT, Wolbers M, et al. Combination antifungal therapy for cryptococcal meningitis. *N Engl J Med*. Apr 4 2013;368(14):1291-1302. Available at <http://www.ncbi.nlm.nih.gov/pubmed/23550668>.
19. Brouwer AE, Rajanuwong A, Chierakul W, et al. Combination antifungal therapies for HIV-associated cryptococcal meningitis: a randomised trial. *Lancet*. May 29 2004;363(9423):1764-1767. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15172774>.
20. Pappas PG, Chetchotisakd P, Larsen RA, et al. A phase II randomized trial of amphotericin B alone or combined with fluconazole in the treatment of HIV-associated cryptococcal meningitis. *Clin Infect Dis*. Jun 15 2009;48(12):1775-1783. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19441980>.
21. Larsen RA, Bozzette SA, Jones BE, et al. Fluconazole combined with flucytosine for treatment of cryptococcal meningitis in patients with AIDS. *Clin Infect Dis*. Oct 1994;19(4):741-745. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7803641>.
22. Bicanic T, Meintjes G, Wood R, et al. Fungal burden, early fungicidal activity, and outcome in cryptococcal meningitis in antiretroviral-naïve or antiretroviral-experienced patients treated with amphotericin B or fluconazole. *Clin Infect Dis*. Jul 1 2007;45(1):76-80. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17554704>.
23. Nussbaum JC, Jackson A, Namarika D, et al. Combination flucytosine and high-dose fluconazole compared with fluconazole monotherapy for the treatment of cryptococcal meningitis: a randomized trial in Malawi. *Clin Infect Dis*. Feb 1 2010;50(3):338-344. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20038244>.
24. Saag MS, Cloud GA, Graybill JR, et al. A comparison of itraconazole versus fluconazole as maintenance therapy for AIDS-associated cryptococcal meningitis. National Institute of Allergy and Infectious Diseases Mycoses Study Group. *Clin Infect Dis*. Feb 1999;28(2):291-296. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10064246>.
25. Powderly WG, Saag MS, Cloud GA, et al. A controlled trial of fluconazole or amphotericin B to prevent relapse of cryptococcal meningitis in patients with the acquired immunodeficiency syndrome. The NIAID AIDS Clinical Trials Group and Mycoses Study Group. *N Engl J Med*. Mar 19 1992;326(12):793-798. Available at <http://www.ncbi.nlm.nih.gov/pubmed/1538722>.
26. Perfect JR, Marr KA, Walsh TJ, et al. Voriconazole treatment for less-common, emerging, or refractory fungal infections. *Clin Infect Dis*. May 1 2003;36(9):1122-1131. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12715306>.

27. Pitisuttithum P, Negroni R, Graybill JR, et al. Activity of posaconazole in the treatment of central nervous system fungal infections. *J Antimicrob Chemother.* Oct 2005;56(4):745-755. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16135526>.
28. Zolopa A, Andersen J, Powderly W, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. *PLoS One.* 2009;4(5):e5575. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19440326>.
29. Makadzange AT, Ndhlovu CE, Takarinda K, et al. Early versus delayed initiation of antiretroviral therapy for concurrent HIV infection and cryptococcal meningitis in sub-saharan Africa. *Clin Infect Dis.* Jun 1 2010;50(11):1532-1538. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20415574>.
30. Boulware DR, Meya DB, Muzoora C, et al. Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis. *N Engl J Med.* Jun 26 2014;370(26):2487-2498. Available at <http://www.ncbi.nlm.nih.gov/pubmed/24963568>.
31. Fessler RD, Sobel J, Guyot L, et al. Management of elevated intracranial pressure in patients with Cryptococcal meningitis. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology: Official Publication of the International Retrovirology Association.* Feb 1 1998;17(2):137-142. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9473014>.
32. Newton PN, Thai le H, Tip NQ, et al. A randomized, double-blind, placebo-controlled trial of acetazolamide for the treatment of elevated intracranial pressure in cryptococcal meningitis. *Clin Infect Dis.* Sep 15 2002;35(6):769-772. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12203177>.
33. Beardsley J, Wolbers M, Kibengo FM, et al. Adjunctive Dexamethasone in HIV-Associated Cryptococcal Meningitis. *N Engl J Med.* Feb 11 2016;374(6):542-554. Available at <http://www.ncbi.nlm.nih.gov/pubmed/26863355>.
34. Shelburne SA, 3rd, Darcourt J, White AC, Jr., et al. The role of immune reconstitution inflammatory syndrome in AIDS-related Cryptococcus neoformans disease in the era of highly active antiretroviral therapy. *Clin Infect Dis.* Apr 1 2005;40(7):1049-1052. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15825000>.
35. Muller M, Wandel S, Colebunders R, et al. Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. *Lancet Infect Dis.* Apr 2010;10(4):251-261. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20334848>.
36. Boulware DR, Bonham SC, Meya DB, et al. Paucity of initial cerebrospinal fluid inflammation in cryptococcal meningitis is associated with subsequent immune reconstitution inflammatory syndrome. *J Infect Dis.* Sep 15 2010;202(6):962-970. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20677939>.
37. Chang CC, Dorasamy AA, Gosnell BI, et al. Clinical and mycological predictors of cryptococcosis-associated immune reconstitution inflammatory syndrome. *AIDS.* Aug 24 2013;27(13):2089-2099. Available at <http://www.ncbi.nlm.nih.gov/pubmed/23525034>.
38. Haddow LJ, Colebunders R, Meintjes G, et al. Cryptococcal immune reconstitution inflammatory syndrome in HIV-1-infected individuals: proposed clinical case definitions. *Lancet Infect Dis.* Nov 2010;10(11):791-802. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21029993>.
39. Kuttiatt V, Sreenivasa P, Garg I, Shet A. Cryptococcal lymphadenitis and immune reconstitution inflammatory syndrome: current considerations. *Scand J Infect Dis.* Aug 2011;43(8):664-668. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21534892>.
40. Brandt ME, Pfaller MA, Hajjeh RA, et al. Trends in antifungal drug susceptibility of Cryptococcus neoformans isolates in the United States: 1992 to 1994 and 1996 to 1998. *Antimicrob Agents Chemother.* Nov 2001;45(11):3065-3069. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11600357>.
41. Witt MD, Lewis RJ, Larsen RA, et al. Identification of patients with acute AIDS-associated cryptococcal meningitis who can be effectively treated with fluconazole: the role of antifungal susceptibility testing. *Clin Infect Dis.* Feb 1996;22(2):322-328. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8838190>.
42. Chen SC, Australasian Society for Infectious Diseases Mycoses Interest G. Cryptococcosis in Australasia and the treatment of cryptococcal and other fungal infections with liposomal amphotericin B. *J Antimicrob Chemother.* Feb 2002;49 Suppl 1(Suppl 1):57-61. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11801583>.
43. Kirk O, Reiss P, Uberti-Foppa C, et al. Safe interruption of maintenance therapy against previous infection with four common HIV-associated opportunistic pathogens during potent antiretroviral therapy. *Ann Intern Med.* Aug 20 2002;137(4):239-250. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12186514>.

44. Vibhagool A, Sungkanuparph S, Moosikapun P, et al. Discontinuation of secondary prophylaxis for cryptococcal meningitis in human immunodeficiency virus-infected patients treated with highly active antiretroviral therapy: a prospective, multicenter, randomized study. *Clin Infect Dis*. May 15 2003;36(10):1329-1331. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12746781>.
45. Mussini C, Pezzotti P, Miro JM, et al. Discontinuation of maintenance therapy for cryptococcal meningitis in patients with AIDS treated with highly active antiretroviral therapy: an international observational study. *Clin Infect Dis*. Feb 15 2004;38(4):565-571. Available at <http://www.ncbi.nlm.nih.gov/pubmed/14765351>.
46. Pursley TJ, Blomquist IK, Abraham J, Andersen HF, Bartley JA. Fluconazole-induced congenital anomalies in three infants. *Clin Infect Dis*. Feb 1996;22(2):336-340. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8838193>.
47. Norgaard M, Pedersen L, Gislum M, et al. Maternal use of fluconazole and risk of congenital malformations: a Danish population-based cohort study. *J Antimicrob Chemother*. Jul 2008;62(1):172-176. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18400803>.
48. Mastroiacovo P, Mazzone T, Botto LD, et al. Prospective assessment of pregnancy outcomes after first-trimester exposure to fluconazole. *Am J Obstet Gynecol*. Dec 1996;175(6):1645-1650. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8987954>.
49. De Santis M, Di Gianantonio E, Cesari E, Ambrosini G, Straface G, Clementi M. First-trimester itraconazole exposure and pregnancy outcome: a prospective cohort study of women contacting teratology information services in Italy. *Drug Saf*. 2009;32(3):239-244. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19338381>.
50. Bar-Oz B, Moretti ME, Bishai R, et al. Pregnancy outcome after in utero exposure to itraconazole: a prospective cohort study. *Am J Obstet Gynecol*. Sep 2000;183(3):617-620. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10992182>.